REMARKS:

The Examiner has asked for an explanation from the applicant regarding the classification of types of diabetes.

As indicated in the enclosed excerpt from "Diabetes in America", Chapter 2, by Maureen I. Harris, diabetes mellitus is traditionally defined as falling into four groups:

1. Insulin-dependent diabetes (IDDM)

2. Non-insulin-dependent diabetes (NIDDM)

and two other groups which need not be reviewed here.

IDDM is also known as Type I diabetes and NIDDM as Type II, as indicated by the WHO classification referred to by the Examiner.

The main distinctions between the two groups are the differing etiology of the disease between the groups and the characteristic dependence on insulin to prevent life-threatening ketosis in Type I diabetes, as contrasted with Type II diabetes which normally does not produce life-threatening ketosis and hence dependence on insulin injections. This is reflected in the characteristics listed in Table 2.1 of the enclosed article.

"Insulin-dependent" is not, however, synonymous with "insulin-requiring", which refers to all diabetics who are unable to avoid hyperglycaemia without the use of insulin (as indicated at page 7, lines 23 to 25 of the specification). Although many NIDDM or Type II diabetics can be treated with oral glycaemic drugs alone, many others require insulin injections to supplement their own endogenous production of insulin and improve the control of their disease.

As evidence, the Examiner is referred to the second paragraph of the enclosed article, which indicates that "insulin-treated NIDDM comprises ~30% of diagnosed diabetes and NIDDM not treated with insulin comprises ~55%".

The Examiner is requested to reconsider the claims of this application in light of the above explanation.

It is also submitted that claims 6 and 7 differ in that claim 7 contemplates a single medicament including insulin and one of the defined peptides, whereas claim 6 contemplates two separate medicaments used in a combined regimen.

Respectfully submitted,

FROM :

DIABETES

IN

AMERICA

2ND EDITION

National Diabetes Data Group

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Chapter 2

Classification, Diagnostic Criteria, and Screening for Diabetes

Maureen I. Harris, PhD, MPH

SUMMARY

Diabetes mellitus comprises a heterogeneous group of disorders characterized by high blood glucose levels. Four major types of diabetes have been defined by the National Diabetes Data Group (NDDG) and the World Health Organization (WHO): insulin-dependent diabetes mellitus (IDDM), non-insulin-dependent diabetes mellitus (NIDDM), gestational diabetes mellitus (GDM), and diabetes secondary to other conditions. Diabetes can be diagnosed by the presence of the classic signs and symptoms of diabetes and unequivocally elevated blood glucose levels, by fasting plasma glucose (FPG) ≥140 mg/dl, or by venous plasma glucose ≥200 mg/dl at 2 hours after a 75-g oral glucose challenge.

In 1993, there were ~7.8 million diagnosed cases of diabetes in the United States, of whom ~43% were treated with insulin. IDDM with onset at age <30 years comprises ~7% of all diagnosed cases. Some studies indicate that ~7% of insulin-treated cases with onset at age ≥30 years may also be IDDM. If these data are correct, then insulin-treated NIDDM comprises ~30% of diagnosed diabetes and NIDDM not treated with insulin comprises ~55%. Diabetes associated with or secondary to other conditions may occur in ~1%-2% of all disorders comprising the syndrome of diabetes. In addition to these diagnosed cases, there are ~7 milli n undiagnosed cases of NIDDM in the United States. GDM occurs in ~3%-5% of all pregnancies.

Impaired glucose tolerance (IGT) is a class that encompasses persons whose glucose tolerance is intermediate between normal and diabetic. About 11% of adults have IGT when tested by oral glucose challenge.

About half of adults with diagnosed NIDDM indicate that they were symptomatic at diagnosis, but the other half report that their diabetes was diagnosed during a routine physical exam, through screening for diabetes, or while being treated for another condition. Virtually all people with NIDDM state that they had a blood test at diagnosis, with 38% indicating that an oral glucose tolerance test (OGTT) had been performed at diagnosis.

About 31% of adults without diagnosed diabetes in 1989 reported being screened for diabetes in the previous year. Blood glucose tests were ordered or performed in 23.5 million visits of patients without diabetes to office-based physicians in 1985, and urine glucose tests in 55.3 million visits. These tests were presumably used in screening for hyperglycemia and glycosuria. About 3.2 million OGTTs were performed annually during 1989-90 during patient visits to office-based physicians.

The onset of NIDDM, on average, is probably ~10 years before clinical diagnosis. A proportion of individuals with undiagnosed NIDDM develop microvascular disease of the eye and kidney and neuropathy during this preclinical period, and macrovascular disease and risk factors for vascular disease are very common in these persons. Consequently, screening for undiagnosed NIDDM appears warranted, particularly in persons at high risk for NIDDM, although controversy exists about screening. Detection of undiagnosed NIDDM can be conducted by an oral glucose challenge or FPG, although only ~25% of adults with undiagnosed NIDDM (2-hour post-challenge glycemia ≥200 mg/dl) have fasting hyperglycemia (≥140 mg/dl).

Screening is most appropriately carried out in groups at high risk for NIDDM. Major risk factors for NIDDM include older age; obesity; family history of diabetes; race/ethnicity of black, Hispanic, or American Indian; and presence of complications related to diabetes. As many as 78% of nondiabetic adults in the United States have at least one of these risk factors, and 23% have three or more. Rates of screening for diabetes are higher in people with these risk factors and with diabetes-related complications. In 1989, 39% of per-

ple with three risk factors or complications, and 57% of people with four or more reported being screened for diabetes in the previous year. If the 75-g oral glucose challenge is used to screen for undiagnosed NIDDM in the U.S. population, the yield of positive screenees (2-hour glucose ≥200 mg/dl) would be 9% when people age ≥40 years who have a percent desirable weight (PDW) ≥120 are screened. This would capture 67% of all U.S. adults with undiagnosed

NIDDM. The yield could be increased to 25% if peop age ≥40 years with PDW ≥140 and a family history diabetes were screened. This would capture only 25 of all cases of undiagnosed NIDDM, but only 6% U.S. adults would have to be administered the or glucose challenge. The cost-effectiveness and lon range benefit to the patient of such screening strat gies remain to be defined.

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CLASSIFICATION AND FREQUENCY OF THE TYPES OF DIABETES

Diabetes mellitus is a clinically and genetically heterogeneous group of disorders that have one common feature—abnormally high levels of glucose in the blood due either to insulin deficiency or to resistance of the body's cells to the action of insulin. It has been centuries since this syndrome was first recognized. However, over the past several decades, research has led to the recognition that the different types of diabetes have different causes although their pathologic courses after onset of diabetes may be similar. The classification of this heterogeneous group of disorders

is summarized in Table 2.1. This classification is re ommended by the NDDG of the National Institutes Health[1] and by the WHO Expert Committee on Diab tes[2,3]. It includes the types of diabetes that occur in th United States but does not include diabetic syndrom common in some countries but rarely seen in th United States, such as malnutrition-related diabete The table highlights the different clinical present: tions and genetic and environmental etiologic facto: that permit discrimination among the types of diab tes.

In patients for whom inadequate information is ol tained, it may be difficult to distinguish among IDDN NIDDM, and diabetes secondary to other diseases. Fr

Table 2.1
Classification of the Types of Diabetes

Class name	Characteristics
Insulin-dependent diabetes mellitus (IDDM)	Low or absent levels of circulating endogenous insulin and dependent on injected insulin to prevent ketosis and sustain life Onset predominantly in youth but can occur at any age Associated with certain HLA and GAD antigens Abnormal immune response and islet cell antibodies are frequently present at diagnosis Etiology probably only partially genetic, as only ~35% of monozygotic twins are concordant for IDDM
Non-insulin-dependent diabetes mellitus (NIDDM)	Insulin levels may be normal, elevated, or depressed; hyperinsulinemia and insulin resistance characterize most patients; insulinopenia may develop as the disease progresses Not insulin-dependent or ketosis-prone under normal circumstances, but may use insulin for treatment of hyperglycemia Onset predominantly after age 40 years but can occur at any age Approximately 50% of men and 70% of women are obese Etiology probably strongly genetic as 60%-90% of monozygotic twins are concordant for NIDDM
Gestational diabetes (GDM)	Glucose intolerance that has its onset or recognition during pregnancy Associated with older age, obesity, family history of diabetes Conveys increased risk for the woman for subsequent progression to NIDDM Associated with increased risk of macrosomia

Other types of diabetes, including diabetes secondary to or associated with:
    Pancreatic disease
    Hormonal disease
    Drug or chemical exposure
    Insulin receptor abnormalities
    Certain genetic syndromes
	In addition to the presence of the specific condition, hyperglycemia at a level diagnostic of diabetes is also present
	Causes of hyperglycemia are known for some conditions, e.g., pancreatic disease; in other cases an etiologic relationship between diabetes and the other condition is suspected

IDDM there may be evidence of insulinopenia by direct measurement of insulin or C-peptide levels, by inference through documentary episodes of ketosis, or by a history of insulin use equal to the duration of diabetes in thin patients. Diabetes secondary to another condition can only be established by clinical workup or medical history to determine the presence of the other condition (see Chapter 5). If IDDM and secondary diabetes can be excluded, patients who meet the diagnostic criteria for diabetes can be presumed to have NIDDM.

in the United States in 1992, by age and type of diabetes, based on self-reported data from the 1989 and 1992 National Health Interview Surveys (NHIS). Women in the survey who had diabetes diagnosed only during pregnancy have been excluded, and the small proportion of subjects with secondary diabetes (-1%-2%) could not be identified.

There are -7.4 million diagnosed cases of diabetes in the United States, based on 1992 estimates of the population[4]. Of these, -43% are treated with insulin[5]. IDDM with onset at age <30 years comprises -7% of all diagnosed cases[5]. Some studies indicate that -7% of insulin-treated cases with onset at age ≥30 years may also be IDDM[6-8]. If these data are correct, then insulin-treated NIDDM comprises -30% of diagnosed diabetes and NIDDM not treated with insulin comprises -55%. GDM occurs in -3%-5% of all pregnancies (see Chapter 35). Diabetes associated with or secondary to other conditions may occur in -1%-2%

of all disorders comprising the syndrome of diabetes (Chapter 5). In addition to these diagnosed cases, there are -7 million undiagnosed cases of NIDDM in the United States, based on the finding that there is about one undiagnosed case for every diagnosed case among adults[9,10].

The heterogeneity within the syndrome of diabetes implied in Table 2.1 has important implications for research and for clinical management of patients. For example, different genetic, metabolic, environmental tions), although the disorders in Table 2.1 differ markedly in pathogenesis, natural history, and responses to therapy and preventive measures. The exact causes of IDDM and NIDDM, the subject of intensive research over the past decades, remain unknown, although both can be accompanied by ketoacidosis, blindness, kidney failure, premature cardiovascular disease, stroke, amputations, and other complications. GDM may arise from the physiological stresses of pregnancy or it may be a degree of abnormal glucose tolerance that precedes pregnancy and is discovered during the routine metabolic testing that occurs during pregnancy (see Chapter 35). Diabetes associated with other conditions may be strictly secondary to the pathophysiology of these conditions (Chapter 5). Each class in Table 2.1 may be heterogeneous in etiology and pathogenesis, and further research is needed to define more precisely the different types of diabetes, determine their etiologies, and devise more appropriate preventive and therapeutic strategies.

Table 2.2
Prevalence of Diagnosed Diabetes (Thousands) According to Type of Diabetes, U.S., 1992

Type of diabetes and insulin use	All	Age group (years)			
		<18	18-44	45-64	≥65
All diabetes	7,417	87	1,214	2,716	3,400
IDDM, onset age <30 years	528	87	375	57	9
IDDM, onset age ≥30 years	535	0	103	201	231
NIDDM, using insulin	2,183	0	285	913	985
NIDDM, not using insulin	4,171	0	451	1,545	2,175

The small proportion of persons with diagnosed diabetes who have secondary diabetes (-1%-2%) could not be identified. All subjects who do not have IDDM have been designated as NIDDM. All subjects age <18 years are assumed to have IDDM. For age ≥18 years, subjects with age at onset <30 years were defined as having IDDM if they had continuous insulin use since diagnosis and percent desirable weight (PDW) <120 (equivalent to BMI of <27 for males and <25 for females). For diabetic subjects with age at diagnosis ≥30 years, 8.5% with current age 30-49 years, 7.4% age 50-64 years, and 6.8% age ≥65 years appear to have IDDM, based on PDW <125 and continuous insulin use since diagnosis of diabetes (Reference 6). These data have been used to compute the prevalence of IDDM with onset at age ≥30 years and to decrease the prevalence of insulin-treated NIDDM by this amount.

Source: References 4-6

> (a) 1 million
- (a) 2 million